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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/610,215	07/05/2000	Walter Gunzburg	2316.2003-000	4735

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BAKER & BOTTS
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

EXAMINER	
LAMBERTSON, DAVID A	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/610,215	GUNZBURG ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,18 and 22-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-11,15 and 22-24* is/are allowed.

6)☒ Claim(s) *12-14 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Action, filed September 2, 2003. Amendments were made to the claims.

Claims 1-15, 18 and 22-24 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, mailed December 31, 2002, that is not addressed in this action has been withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 18 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for introducing a nucleotide sequence into target cells *in vitro* for the expression of a nucleotide sequence, does not reasonably provide enablement for a method of gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. **This rejection is maintained for the reasons set forth in the previous Office Action**.

It is noted that the substance of this rejection is essentially the same as that for the previous Office Action. However, both the grounds of the rejection (corrected above) and the scope of the invention (indicated below in the *In re Wands* analysis) were improperly indicated.

Specifically, the rejection improperly indicated that expression of a gene *in vivo* was enabled. This indication is withdrawn because such a method reads on gene therapy, which as set forth below and in the previous Office Actions, is not enabled. Thus the repetition of the grounds of the rejection is simple set forth to correct the previous indication of an enabled *in vivo* expression.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Nature of the invention. The Nature of the invention is a method of introducing *any* nucleotide sequences into *any* target cells. Since there is no limitation with regards to the nature of the target cells, these cells can be located in a human being, and since the instant specification is primarily concerned with delivery of transgenes to humans as part of gene therapy, the claims read on a method of gene therapy.

Scope of the invention. The scope of the invention is very broad, encompassing a method of introducing any nucleotide sequence into any type of target cells. This includes cells that are located within a human being, thereby reading on a method of gene therapy. Therefore, while the claimed invention is enabled for the introduction and expression of nucleic acid sequences *in*

vitro, the claimed invention is not enabled for the entire scope of the target cells as indicated because it is not enabled for a method of gene therapy.

State of the art. The state of the art regarding gene therapy techniques is very underdeveloped and unpredictable, owing to a documented lack of success regarding gene therapy treatments. The major obstacles surrounding the lack of success of gene therapy in general, as well as with regard to retroviral vectors and gene therapy, are clearly indicated in the Office Action mailed on October 2, 2001, and will not be repeated for brevity purposes. As these obstacles have not been overcome in the prior art, the skilled artisan cannot turn to the prior art for guidance in practicing the invention.

Number of working examples and Guidance provided by applicant. The instant specification does not overcome the deficiencies documented in the prior art, and no working examples are provided concerning the use of the specific retroviral vector of the instant invention in gene therapy protocols. As a result, the skilled artisan cannot turn to the instant specification for guidance in practicing the invention as claimed.

Level of skill in the art. The level of skill in the art is underdeveloped with regard to the use of retroviral vectors in gene therapy. For example, specific parameters regarding the use of vectors for effective delivery of nucleic acids to target cells during gene therapy and sustained gene expression, as well as an ability to predict and overcome the potential deleterious effects of gene therapy, are unavailable in the art.

Unpredictability of the art. While the specification is enabling for introducing a nucleotide sequence into target cells *in vitro*, introducing genes for therapeutic purposes is not enabled because of the deficiencies surrounding gene therapy practices (see Verma *et al.*, Nature **389**:

239-242 (1997) for review, cited in the previous Office Action mailed on October 2, 2001, and applied as such). In addition, a review by Anderson (*Nature* **392**: 25-30, 1998; see entire document) focuses on the promise and problems specifically facing human gene therapy using retroviral vectors, pointing out that the "problems that investigators face in developing retroviral vectors that are effective in treating disease are of four main types: obtaining efficient delivery, transducing non-dividing cells, sustaining long-term gene expression, and developing a cost-effective way to manufacture the vector" (page 25, right-hand side, first full paragraph). Furthermore, it has been established that "results of clinical trials have been disappointing" because "[E]ven the most successful trial has fallen short of therapeutic efficacy" (Kmiec, *American Scientist* **87**: 240-247, 1999; see entire document, especially page 240, the center column). In consideration of the highly underdeveloped level of skill of the skilled artisan and the deficiencies in the prior art and the instant specification with regard to effective gene therapy procedures, the skilled artisan would be forced to practice undue and unpredictable trial and error experimentation when practicing the invention as claimed.

The amount of experimentation required to practice the invention commensurate with the scope of the claims would be undue in light of the *In re Wands* factor analysis provided above and as referenced to the previous Office Action therein. As a result, it is established that the invention is not enabled with regard to the full scope of the claims.

Response to Arguments Concerning Claim Rejections - 35 USC § 112

Applicant's arguments filed September 2, 2003 have been fully considered but they are not persuasive. Applicant's arguments consist of the following points:

1. That the examiner is interpreting the claim as reading on a method of treating by gene therapy, although the method could be used for other purposes such as ablating cells to create a disease model system.

2. That the enablement standard should be applied to the step of introducing a gene of interest, not the ultimate objective of said introduction.

3. That there is no reason to believe that the introduction of EGFP would not be representative of the introduction of any other gene.

Applicant's arguments have been fully considered but are not found convincing for the following reasons:

1. The instant claim reads on a method of introducing a nucleotide sequence into target cells, this is a very broad claim that includes cells within an organism. Similarly, a method of gene therapy is the process of introducing a nucleotide sequence into a target cell, thus a method of gene therapy is a species within the instant claim. In other words, a method of gene therapy is within the scope of the instantly claimed invention. In this particular instance, the examiner is not solely interpreting the claimed method as reading on a method of treating by gene therapy, as suggested; the examiner is simply interpreting the claimed method as broadly as reasonably possible, and this includes a method of gene therapy. This is evident from the fact that the rejection applied was a "scope of enablement" rejection where a method of gene therapy is specifically indicated as not enabled. It is clearly acknowledged that there are embodiments of the claimed method that are enabled. However, because the claims clearly read on a method of gene therapy, and because the specification repeatedly indicates gene therapy as a particularly

useful embodiment of the claimed method, it is appropriate to reject the method as being claimed too broadly in scope because the instant specification does not teach the skilled artisan how to use the claimed method of "introducing a nucleotide sequence into target cells" as it relates to gene therapy.

2. It is asserted that the rejection is based on a "method of introducing a nucleotide sequence into a target cell" and not solely on a method of gene therapy. However, as indicated above, the method encompasses a method of gene therapy, thus the full scope of the claim is not enabled. This is clearly indicated above.

3. It is agreed that it would be perfectly acceptable to express virtually any gene of interest in an isolated host cell; for example, as it regards specific purposes such as recombinant protein expression, expression of a marker sequence, etc. However, this does not change the fact that the claim is still not enabled for the full scope of the invention, which includes a method of gene therapy.

In conclusion, the examiner has maintained the rejection because the broad scope of the claimed method encompasses gene therapy techniques, and these techniques are not enabled. The examiner also acknowledges that there are embodiments within the claimed method that are enabled. However, while the claim still reads on the clearly non-enabled method of gene therapy, the rejection must be maintained.

New Rejections

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 12-13 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. **This is a new rejection necessitated by amendment.**

Specifically as it regards claim 12, although the claimed retroviral provirus is procured from a host cell that has been infected by a retroviral particle containing the instantly claimed vector, the claimed retroviral provirus can result from a retrovirus that is already endogenous to the host cell. In other words, if the infected target cell contained a retrovirus already present in the cell, the claimed retroviral provirus would in fact not be the result of the specific retroviral particle containing the instantly claimed vector. It would be remedial to indicate that the retroviral provirus claimed was "recombinant" to clearly indicate the provirus results from an infection of a host cell by the instantly claimed retroviral particle containing the instantly claimed vector, and does not result from an endogenous retrovirus.

Specifically, as it regards claim 13, the claim simply reads on any mRNA sequence. The claimed vector can reasonably contain any coding sequence (see for example Applicant's own arguments on page 8, third full paragraph, in response to the previous Office Action; "There is no reason to believe that introduction of the *egfp* gene would not be representative of introduction of any other gene..."). Thus, the mRNA produced from the retroviral provirus containing a retroviral vector with any coding sequence in it would read on all mRNAs in any cell. Since there is no chemical distinction between an mRNA produced from the retroviral

particle/vector of the instantly claimed invention and an mRNA endogenous to any host cell, the mRNA is non-statutory as not demonstrating the presence of the "hand-of-man."

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection necessitated by amendment.**

Claim 12 is indefinite because it is unclear if the claims are directed to a provirus that results from the infection of a target cell solely with the retroviral vector of claim 1, or if it includes provirus that can be acquired from a host cell that is also infected with an endogenous retrovirus. See also the rejections under 35 USC § 101. It would be remedial in this instance to indicate the retroviral provirus was "recombinant."

Claim 14 is indefinite for the recitation of the limitation "RNA of a retroviral vector." It is unclear if the claim includes an RNA that can be produced from the vector after host cell integration (i.e., does it include an mRNA produced by the vector after integration). It is also unclear if the RNA includes any portion of an RNA (i.e., a diribonucleotide sequence, a 3' or 5' LTR, etc.), or if it must include the entire reverse transcribed sequence of the claimed vector. Because it is unclear what constitutes an RNA of a retroviral vector, the claim is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Alexander *et al.* (*Biotechniques* **23**: 64-66, July 1997; see entire document; henceforth Alexander). **This is a new rejection necessitated by amendment.**

Claim 13 is directed to an mRNA of a retroviral provirus, where the provirus is generated by infecting cells with a retroviral particle comprising the retroviral vector of claim 1. Although claim 1 is free of the art, and therefore the retroviral particle is free of the art, the mRNA of claim 13 is not free of the prior art because it is similar to a product-by process claim. Also, see the rejections under 35 USC § 101. Applicant is effectively claiming any mRNA that can be produced by the vector; in other words, applicant is claiming any mRNA for the "one or more coding sequences" that are placed in the vector. In the specification, applicant uses EGFP as an example of a coding sequence that can be placed in the vector, where this coding sequence is transcribed into an mRNA and expressed in infected cells (therefore, it would be present in the provirus that are generated by the infected cells). Alexander teaches the expression of EGFP from a retroviral vector, thereby teaching an EGFP mRNA (see for example 64, left column). As there is no clear chemical distinction between this EGFP mRNA and the EGFP mRNA that would be produced from the instantly claimed provirus, the invention of claim 13 is anticipated.

Claim 14 is directed to any RNA of the retroviral vector of claim 1. The claim is interpreted to include an RNA for the 3'LTR, the 5'LTR, etc., of a retroviral vector (see also the

rejections under 35 USC § 112, second paragraph). These elements are present on virtually every retroviral vector, including pLXSG and pLnefSG vectors disclosed in Alexander (see for example Figure 1, page 64). Although the RNA (in the form of the 3' and 5' LTRs) taught by Alexander do not come from the instantly claimed vector, the instantly claimed vector includes any 3' or 5' LTR sequence; thus, a particular RNA coming from the instantly claimed vector would be indistinguishable from the 3' or 5' LTR of the vector taught by Alexander. This is similar to a product-by-process claim, where the instantly claimed RNA is a product of the reverse transcription process that must be performed on the instantly claimed vector in order to produce an RNA. Therefore, Alexander teaches an RNA of the vector of claim 1 (such as a 5'LTR) because the 5'LTR would be identical to the 5'LTR from the instantly claimed vector, considering the broad scope of the instantly claimed vector..

Allowable Subject Matter

Claims 1-11and 22-24 are allowed.

Claims 12-14 and 18 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson, Ph.D.
AU 1636

JAMES KETTER
PRIMARY EXAMINER